II. REMARKS

Applicants acknowledge with appreciation the Examiner's withdrawal of the restriction requirement under 35 USC §§121 and 372, as set forth in the January 27, 2003 Office Action. Prior to amendment, claims 1-7 were pending in this application. Claims 5 and 6 have been cancelled, claim 7 has been amended and new claims 8-12 have been added herein. Claims 1-4 and 7-13 will be pending upon entry of the amendment. Initially submitted claims 1-7 stand rejected under 35 U.S.C. §112, first and second paragraphs.

A. The Amendments

Applicants have cancelled claim 5 and added a new claim 8, as a step-for claim with §112, sixth paragraph, limitations. Claim 6 has been cancelled and a new dependent claim 9 has been added that claims the same method as contained in the cancelled claim 6. Claim 7 has been amended for clarity and definiteness. New claims 8 and 9 are supported in the specification on page 3, lines 14-23, page 5, lines 21-31, page 6, line 1-10 and Example 6, page 21. Additionally, new claims 10-12 are supported on page 3, lines 28-30, page 4, lines 1-6 and lines 17-26, page 5, lines 24-26, page 8, lines 14 and page 11, lines 24-27.

The amendments and new claims are fully supported in the application as filed and no new matter is added hereby. Applicants respectfully request that the amendments be entered in the application.

B. Rejection Under 35 U.S.C. § 112, First Paragraph

In the Office Action, dated July 30, 2003, claims 1-7 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enabling written description requirement. It was asserted that the claim(s) contained subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention.

Specifically, the Examiner pointed out several phrases occurring in the claims that were alleged to lack enablement in the written description of the specification. The following points were raised and are each discussed below.

a) It was asserted that there was no descriptive support in the specification for the term "activating reagent" used in the claims 5 and 7. Further, it was asserted that there was no indication in the specification what component(s) were required constituents of the "activating reagent" in claims 5 and 7. See Office Action, pages 2 & 3.

Applicants have cancelled claim 5 and amended claim 7 to provide more clarity commensurate with the scope of the invention. Hence, the phrase "activating reagent" has been replaced by "means for activating" and a new claim 8 has been added as a "step-for" claim with §112, sixth paragraph, limitations. "An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof". See 35 USC 112, sixth paragraph. Thus, Applicants respectfully request that this rejection be withdrawn.

b) It was asserted that the term "a label containing *an amine* **or** a carboxyl group" was inconsistent with the enabling written description of the invention of page 8, lines 1-8, of the specification citing " 'a carboxyl group' on the 'label' was required whereas the presence of an 'amine group' was undesirable ('preferably the label moiety does not have free amines')." Further, it was asserted that for all claims enablement was present only for the use of "labels" which contained carboxyl groups. See Office Action, page 3.

Applicants respectfully traverse this rejection on two grounds. First, the specification expressly discloses labels that could contain a free amine or a carboxyl group. The specification on page 8 describes various types of labels such as phycobiliproteins, enzymes, recombinant or native protein fluors and organic dyes with free amines. Applicants direct the attention of the Examiner to Example 1 where the two proteins phycoerythrin (PE) and streptavidin (SA) were conjugated using sulfo-NHS activation. It is well known in the literature that the label phycoerythrin is a large proteins (~240 kd) containing both carboxyl and amine reactive functionalities. Thus, one of ordinary skill in the art would be able to understand that a "label containing an amine or a carboxyl group" to imply that the label need not only contain a carboxyl group but may just as well contain an amine group.

Second, while it is true that the carboxyl group forms the activating NHS ester with carbodiimide suitable for nucleophilic attack by an amine, a label with free amine can also be

activated and cross linked with proteins using heterofunctional reagents such as SMCC and SPDP. The specification on page 4 describes SMCC and SPDP pre-activated phycobiliproteins. Further, specification on page 5 teaches the method of cross linking labels with targets using SMCC, a heterobifunctional reagent that cross links amines (NH_2) of the label with sulfhydryl (SH) groups of the target protein.

Additionally, the specification on page 8, lines 5-8, teaches that amines on the label could be converted to carboxyl groups (in the case of acetic anhydride) or other groups non-reactive with the NHS such as thiols (e.g., SATA). See Example 6 for a comparison of SMCC/SATA cross-linking reaction with sulfo-NHS/EDAC reaction. One skilled in the art would be able to understand that there is adequate written description for enablement for labels containing either an amine or a carboxyl group. Therefore, Applicants respectfully request that this rejection be withdrawn.

c) It was asserted that there was no enabling written description in the specification to support the method of claim 5d, i.e. "removing the activating reagent in the presence of a target moiety, whereby the target moiety is conjugated to the label." It was asserted that it was not clear that "removing the activating reagent would cause the "target moiety" to be conjugated to the "label". See Office Action, page 3.

Since claim 5 has been cancelled, Applicants respectfully request that this rejection be withdrawn.

d) It was asserted that there was no enabling written description in the specification to support the generic concept of claim 6 and that support in the specification was limited to the method described at page 5, lines 21-31 which used SMCC and specific "reductants". It was further asserted that the disclosure on page 8 of the types of labels with amine functionalities were undesirable and therefore this was inconsistent with claim 6a, that "derivatizing a label containing a primary or secondary amines." It was also asserted that it was not clear as to what moiety the "reductant" reduced. See Office Action, page 3.

Although claim 6 has been cancelled, Applicants respectfully traverse this rejection as new claim 9 contains the same method as in claim 6. Applicants submit that the disclosure on page 8, teaches suitable labels that preferably have no free amines. These labels are chosen

specifically for the method of conjugation involving the NHS-ester activation chemistry to couple labels to proteins with free amines *via* an amide linkage. However, here claim 6a (or new claim 9) is describing an alternate method of conjugating label to target moiety wherein a heterobifunctional reagent is used for coupling. Common heterobifunctional reagents such as SMCC can react not only with amines *via* the NHS-ester functionality but also with sulfhydryl group (SH) *via* the maleimide functionality in the presence of reductants. Applicants direct the attention of the Examiner to page 5 of the specification on lines 21-28. Here, the Applicants disclose the use of SMCC to conjugate labels to proteins. SMCC is a heterobifunctional reagent that is capable of reacting with the free primary and secondary amines on the label. Once the NHS ester part reacts, the reagent still has another reactive functionality (the maleimide group) that can couple to a sulfhydryl group (SH) of the target protein. .

Further, the specification on page 5, line 27 discloses the common "reductants" such as dithiothreitol or β-mercaptoethanol. One skilled in the art would know that these reductants are capable of reducing disulfide (S-S) bonds in the target protein to create sulfhydryl (SH) groups, which react and couple to the maleimide functionality of the SMCC forming a thioether covalent linkage. Therefore, Applicants respectfully request that this rejection be withdrawn.

e) It was asserted that there was no enabling written description to support the method of claim 6d, "removing the reductant in the presence of a target moiety, whereby the target moiety is conjugated to the label." It was further stated that it was not clear that removing the reductant would cause the target moiety to be conjugated to the label. See Office Action, page 3.

Although claim 6 has been cancelled, the new claim 9d still retains the same language as used in the cancelled claim 6d. Applicants respectfully traverse this rejection. Applicants direct the attention of the Examiner to specification on page 5 line 25-31, wherein the specification teaches that the reductants such as DTT and β-mercaptoethanol were used and hydrated in the presence of the protein to be conjugated. It is well known in the chemical literature that this procedure activates the protein by forming sulfhydryl groups, and upon removal of this reductant through dialysis, the sulfhydryl group can couple with the maleimide group of the heterofunctional reagent. For example, see the "Anfinsen experiment" described in the journal *Science* 181, 223-230 (1973) for reduction of disulfide bonds with mercaptoethanol, dialysis and subsequent protein refolding process.

Further, the Federal Circuit has held that "...not everything necessary to practice the invention need be disclosed. In fact what is well known is best omitted." *In re Buchner*, 929 F. 2d (Fed. Cir. 1991). "...All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art...the scope of enablement must only bear a "reasonable correlation" to the scope of the claims." See, e.g., *In re Fisher*, 427 F.2d 833 (CCPA 1970). MPEP 2164.08. Thus, Applicants respectfully request withdrawal of this rejection because the method of claim 6 is broadly supported in the specification and one skilled in the art would be readily able to infer the terms in claim 6 to refer to the conjugation reaction.

f) It was asserted that the specification fails to define the word "target" and the enabling written description in the specification was limited to description of page 4, lines 7-9. See Office Action, page 3. Applicants respectfully traverse this rejection.

Applicants direct the attention of the Examiner to page 3, lines 14-16, wherein the specification teaches that the invention is directed to simplified methods of coupling labels to particular target moieties. It states, "such coupling is usually accomplished by activating the label, the 'target moiety', or both with highly reactive activating chemicals." Further, on page 3 lines 28-30, the specification recites that all reactants are prepared separately, then combined in such a way that they do not react with each other until the "targeted compound" is added to activate the cross-linking chemicals. Likewise, on page 5 lines 4-5, the specification teaches that the method of invention allows a person to add a target moiety to be labeled (e.g., a protein provided in a buffered solution) to a dry powder containing a detectable label..." Additionally, page 12, lines 1-6, of specification recites that suitable target moieties include receptors, antibodies, nucleic acids, etc. Also, examples 1, 5 and 7 describe the coupling reaction which involve coupling to a target protein. Thus, Applicants submit that there is ample description and examples of the word "target" in the specification to refer to a moiety which a label couples to in the final conjugation reaction.

As discussed in **(e)** above, the Federal Circuit has held that "All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art and the scope of enablement must only bear a 'reasonable correlation' to the scope

of the claims." See, e.g., *In re Fisher*, 427 F.2d 833 (CCPA 1970). MPEP 2164.08. Thus, Applicants respectfully request that the enablement rejection be withdrawn.

C. **Rejection Under 35 U.S.C. § 112, Second Paragraph**

Claims 1-7 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. See Office Action, page 4. Specifically, the following issues were raised.

a) It was asserted that claim 2 was confusing and incomplete because although the claim was drawn to a method for conjugating label to target moiety there was no step wherein the target moiety was added. See Office Action, page 4.

Applicants respectfully traverse this rejection. Applicants direct the Examiner's attention to page 5, lines 4-9, wherein the specification describes the method of reaction. It teaches that the method allows a person to add a target moiety to be labeled to a dry powder containing a detectable label such that once the dry powder is hydrated, a reactive NHS ester is created that links the detectable label to the target protein in a single step. Further, the specification on page 5, lines 12-20, describes the kit form where the reactants are frozen in a sequential manner and upon rehydration a reaction is created to make usable conjugate of the label with the target protein. See examples 1, 5 and 7 for the rehydration of the dried reagents in the presence of the target moiety e.g. a protein in a buffered solution. Thus, one skilled in the art would be able to understand that hydrating the dry powder in the buffer solution containing the target protein is actually the step of adding the target moiety for conjugation. Furthermore, claims 3 and 4, both of which depend from claim 2, recite variations of the claimed method in which the target is added at different stages of the process.

The definiteness requirement of §112 entails assessing "whether the claim meets the threshold requirement of clarity and precision, not whether more suitable language or modes of expression are available. ...Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the Examiner might desire." MPEP 2173.02. Further, "In reviewing a claim for compliance with 35 USC §112,

second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope, and, therefore, serves the notice function required by 35 U.S.C. §112 second paragraph." See, e.g. *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372 (Fed. Cir. 2000). MPEP 2173. 02. Thus, Applicants respectfully request that this rejection be withdrawn.

b) It was asserted that in claim 5, step **b,** the phrase "its reaction partner" including the terms "its" and "reaction partner" were unclear. The same assertion was extended to claim 7, which contained the same terms. Although claim 5 has been cancelled, new claim 8 (ii) retains the terms. Applicants respectfully traverse this rejection.

Applicants direct the Examiner's attention to page 5, lines 21-31, wherein the specification describes a method of crosslinking a protein using SMCC. (SMCC is a known heterofunctional reagent with NHS and maleimide functionalities that can react to labels and target proteins that have either a carboxyl or a sulfhydryl groups.) Thus, once the heterofunctional reagent is derivatized by the heterofunctional reagent, the heterofunctional reagent has another unreacted functionality through which it can couple to a target moiety. Literally, the term "reaction partner" refers to the chemical partner with which the unreacted functionality of the heterofunctional reagent reacts with. The term "its" is used in the ordinary sense to refer back to the heterofuntional reagent used in the coupling process. One skilled in the art would understand that this term "reaction partner" is commonly used to designate the reacting chemical species that can react with the unreacted functionality of the heterofunctional reagent, e.g., target protein. Thus, Applicants respectfully request the Examiner to withdraw this rejection for the same reasons as discussed in section **(a)** *supra.*

c) It was asserted that in claim 5, step **c**, there was no antecedent basis for the term "label". See Office Action, page 4. Applicants have cancelled claim 5 and have added new claim 8 that more clearly points out and distinctly claims the subject matter of the invention. Claims 8 now reads "derivatized label" in place of "label" in keeping with the definiteness requirement. Thus, Applicants respectfully request that this rejection under §112, second paragraph, be withdrawn.

d) It was asserted that in claim 5 the term "activation" was unclear. Further, it was asserted that there was no requirement that the "activating agent" activate for the purpose of attaching the

"target moiety". This same assertion was made with respect to claim 7. See Office Action, page 4.

Applicants have cancelled claim 5 and amended claim 7 to more clearly point out and distinctly claim the subject matter of the invention. Claim 7 has been amended and a new claim 8 has been added. Accordingly, in a "step for" claim, "...under certain circumstances the written description does not have to explicitly describe the structure (or materials or acts) corresponding to a means-(or step-) plus-function limitation to particularly point out and distinctly claim the invention as required by 35 U.S.C. § 112, second paragraph." See *Dossel*, 115 F.3d at 946. MPEP 2181. Means or step-for performing the specified steps are disclosed in the specification at least on pages 3, 5, 6, 8, 11 and 21. Thus, Applicants respectfully request that this rejection be withdrawn.

e) It was asserted that the term "activating agent" and the type of "activation" intended were unclear. See Office Action, page 4.

Applicants have cancelled claim 5 and the term "activating reagent" has been omitted. However, Applicants direct the Examiner's attention to the disclosure in the application as filed on page 2, lines 11-12. Here, the specification states N-hydrosuccinimide (NHS) esters provide one of the most common activation chemistries for creating acylating agents. Further, on page 3, lines 15-16, the specification recites that coupling is usually accomplished by activating the label, the target moiety, or both with highly reactive activating chemicals. Since a person of ordinary skill in the art would understand activation to refer to an intermediate means for attaching a label to a target protein, Applicants respectfully request that this rejection be withdrawn.

f) It was asserted that it was unclear what the "reductant" of claim 6(**b**) reduced. See Office Action, page 4.

Applicants respectfully traverse this rejection. Applicants direct the Examiner's attention to page 5, lines 26-27, where the reductants disclosed herein are dithiotreitol (DTT) or β-mercaptoethanol. As discussed above, these reagents are commonly used to reduce disulfide bonds (S-S) in proteins and a person of ordinary skill in the art would be able to infer that the reductants reduce these bonds to provide the sulfhydryl (SH) functionality for the coupling

reaction. Thus, Applicants respectfully request that this rejection be withdrawn for the same reasons as explained above.

g) It was asserted that the term "target moiety" as used in the claims was unclear. See Office Action, page 4. Applicants respectfully traverse this rejection.

Applicants direct the Examiner's attention to page 5, lines 4-5 wherein the specification states that the method of invention allows a person to add a target moiety to be labeled (e.g., a protein provided in a buffered solution). Page 12 lines 1-6 of the specification describes a list of suitable target moieties, which includes proteins, nucleic acids and antibodies. Thus, a person of ordinary skill in the art would be able to infer that the terms "target moiety" as used in the claims refers to any compound that the label is intended for conjugation. "Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the Examiner might desire." MPEP 2173.02. Thus, Applicants respectfully request that this rejection be withdrawn for the same reasons as discussed above.

h) It was asserted that in claim 6b it was unclear whether either the "maleimide derivatized label" or the "reductant" or both were required to be in dry form. See Office Action, page 4.

Although claim 6 has been cancelled, new claim 9b retains these expressions. Applicants respectfully traverse this rejection and direct the attention of the Examiner to page 5 lines 24-29 wherein the specification describes sequentially freezing and freeze-drying the SMCC derivative and the reductant. Thus, one skilled in the art would be able to infer that the term both the "maleimide derivatized label" and the "reductant" are in dry form.

Further, in a step-for claim, "...disclosure of structure corresponding to a step-plus function limitation may be implicit in the written description if it would have been clear to those skilled in the art what structure must perform the function recited in the means-plus-function limitation." MPEP 2181. Thus, Applicants respectfully request that all of the above rejections for indefiniteness on the grounds for using unclear terms in the claims be withdrawn.

REQUEST FOR ALLOWANCE

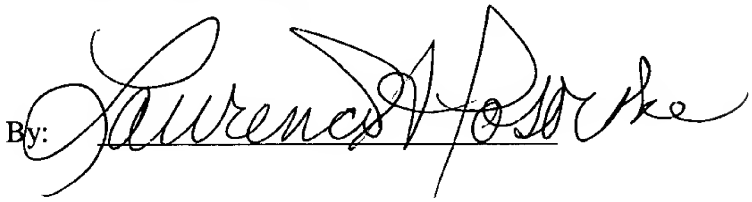
Applicants earnestly solicit reconsideration of the application in view of these remarks. Applicants respectfully submit that in view of the above amendments and remarks, this

application is in condition for allowance and respectfully request an early notification of allowance for the claims as amended herein. If any further action is necessary to place this application in condition for allowance, Applicants would appreciate a telephone call to the undersigned counsel to resolve such issues in a expeditious and effective manner.

Respectfully submitted,

HUNTON & WILLIAMS

Dated: October 27, 2003

By: 

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